REMARKS

Amendments to the Claims

Claims 1, 5 and 11-13 have been canceled.

Claims 3, 4, 7 and 8 have been amended.

New Claims 14-19 have been added.

Claims 3, 4, 7 and 8 have been amended to recite "TNFα-mediated psoriasis." Support for these claim amendments is found in the specification, for example, at page 16, lines 15 to 25 and page 58, line 1 to page 59, line 14.

Claim 3 has been further amended to recite "...administering to the human an effective tumor necrosis factor alpha (TNFα)-inhibiting amount of chimeric anti-TNFα monoclonal antibody cA2." Support for the amendment to Claim 3 is found in the specification, for example, at page 10, lines 8-15 and page 19, lines 7-24.

Claim 4 has been further amended to recite "...administering to the human at least one chimeric anti-TNFα monoclonal antibody cA2...." Support for the amendment to Claim 4 is found in the specification, for example, at page 10, lines 8-15 and page 19, lines 7-24.

Claims 7 and 8 have been further amended to recite "...administering to the human an effective tumor necrosis factor alpha (TNFα)-inhibiting amount of an anti-TNFα chimeric antibody, wherein said anti-TNFα...." Support for the amendment to Claims 7 and 8 is found in the specification, for example, at page 10, lines 8-15 and page 19, lines 7-24.

New Claim 14 is directed to the method of Claim 3 wherein the chimeric anti-TNFα monoclonal antibody cA2 is administered to the human by means of parenteral administration. New Claim 15 is directed to the method of Claim 3 wherein the chimeric anti-TNFα monoclonal antibody cA2 is administered to the human by means of intravenous administration, subcutaneous administration or intramuscular administration. New Claim 16 is directed to the method of Claim 3 wherein the chimeric anti-TNFα monoclonal antibody cA2 is administered to the human orally. Support for these New Claims is found in the specification, for example, at page 59, lines 23-29.

New Claim 17 is directed to the method of Claim 3 wherein said TNFα-inhibiting amount of the chimeric anti-TNFα monoclonal antibody cA2 comprises a single or divided dose of about 0.1 - 50 mg/kg. New Claim 18 is directed to the method of Claim 17 wherein the single or divided dose is selected from the group consisting of: about a 0.1 - 1 mg/kg dose, about a 1.0 -

5 mg/kg dose, about a 5 - 10 mg/kg dose and about a 10 - 20 mg/kg dose. Support for these New Claims is found in the specification, for example, at page 60, lines 7-24.

New Claim 19 is directed to the method of Claim 3 further comprising administering to the human an effective amount of a therapeutic agent selected from the group consisting of: radiotherapeutics, cytotoxic drugs, monoclonal antibodies, chimeric antibodies, antibody fragments, antibody regions, lymphokines, cytokines, hemopoietic growth factors and immunoglobulins. Support for New Claim 19 is found in the specification, for example, at page 62, lines 4-23 and page 63, lines 3-7.

No new matter has been added by this amendment. Therefore, entry of this amendment into the application is respectfully requested.

Supplemental Information Disclosure Statement

Applicants thank the Examiner providing copies of the initialed PTO-1449 Form for the Information Disclosure Statement (IDS) which was filed on October 30, 2001 and the Supplemental IDS's which were filed on March 29, 2002, August 26, 2002, and October 9, 2002. Applicants note that the Examiner acknowledged the PTO Form-1449 for each of the IDSs, but the Examiner has not yet acknowledged the "Related Applications" section, disclosing pending applications, for each IDS. Applicants respectfully request that the Examiner acknowledge this section, which is found on page 2, for each IDS in the next Office Action.

Interview Summary

Applicants thank the Examiner for forwarding the Interview Summary (PTO Form-413), which was attached to the Office Action. In the Interview Summary, the Examiner states that he requested copies of all IDSs filed in the application to complete the record and that the references were not all available at that time. Accordingly, Applicants are submitting herewith copies of all of the Information Disclosure Statements, including PTO-1449 Forms and postcards, filed in the present application.

Form U.S. PTO-892

Applicants note that the Examiner has checked off the box on the Office Action Summary indicating that a record copy of Form PTO-892 was enclosed. However, Applicants did not

receive a copy of Form PTO-892. Applicants request that the Examiner forward the copy of Form PTO-892 with the next Office Action.

Priority

The Examiner maintains that the filing date of the instant claims is deemed to be the filing date of the priority application USSN 08/570,674, filed December 11, 1995, on the grounds that the previous priority applications do not support the claimed limitations of the instant application, encompassing methods of treating psoriasis. The Examiner further states that "...the generic disclosure of treating chronic inflammatory diseases[ ] does not provide sufficient written description for the recitation of the species 'psoriasis, even if 'psoriasis' was considered a chronic inflammatory condition at the time the invention was made."

Applicants respectfully disagree. The instant claims are entitled to claim the benefit of priority application USSN 07/670,827 (filed March 18, 1991). Priority application USSN 07/670,827 provides sufficient written description and enablement for treating TNFα-mediated human disease, including psoriasis. USSN 07/670,827 discloses that the "[h]igh affinity chimeric anti-TNFα mAbs of the present invention, which have potent TNFα neutralizing activity, including TNFα-neutralizing fragments thereof, are useful as therapeutic agents for TNFα-mediated human disease...." (page 10, line 22-25) This priority application teaches treatment of a representative number of species of the genus of "TNFα-mediated diseases," including "rheumatoid arthritis," "Crohn's disease," "sarcoidosis" and "alcohol-induced hepatitis." (page 10, line 22 to page 11, line 4) In addition, the specification of this priority application enables treatment of "TNFα-mediated diseases" with the claimed antibodies. (See USSN 07/670,827 at page 39, line 20 to page 40, line 9 and page 10, lines 22 to page 11, line 4))

Psoriasis is a TNFα-mediated disease. For a clear understanding of the definition of psoriasis, please see Fauci, A. S. et al., Harrison's Principles of Internal Medicine 300 (McGraw-Hill, 14th ed. 1998) (hereinafter "Harrison's"), which was attached as Exhibit A in the Amendment filed on February 25, 2004. Harrison's teaches that psoriasis is a chronic inflammatory disease. Although there is not a specific example in the 07/670,827 specification directed to treatment of TNFα-mediated psoriasis, the mechanism of treatment would be the same regardless of the TNFα-mediated disease.

Therefore, the priority application 07/670,827 provides sufficient written description and

enablement for treating psoriasis, and Applicants are entitled to claim the benefit of it. This priority application has been properly referenced on page 1 of the specification in compliance with 35 U.S.C. § 120.

Further, at the very least, Applicant's are entitled to priority to March 18, 1992. Applicants note that the Examiner cited Applicants' own PCT application Le *et al.* (WO 92/16553) as prior art. The Examiner states that "Claims 1, 3-5, and 7-13 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Adair *et al.* (U.S. Patent No.: 5,994,510) in view of Le *et al.* (WO 92/16553) for the reasons of record." Applicants' PCT application is substantially identical to the corresponding U.S. priority application (USSN 07/853,606) of the subject application, which was filed on the same date as the PCT application (March 18, 1992).

Therefore, if Applicant's disclosure in the PCT application (WO 92/16553) is sufficient to qualify as prior art, then Applicants' disclosure in the March 18, 1992 U.S. priority application (USSN 07/853,606) is sufficient to support the claims, and the claims, at the very least, are entitled to the benefit of priority to the filing date of March 18, 1992.

The Examiner states that "[l]imitation of a class, generically disclosed, to a subgenus without any teaching of the subgenus is new matter unsupported by the specification. *Ex parte Batchelder*, 131 USPQ 38, 39 (1960)." However, *Batchelder* is inapposite because the issue in *Batchelder* related to the ingredient of a claimed chemical composition employed as a solid propellant, wherein examples of other ingredients in the specification did not support or represent the claimed chemical subclass. In addition, the Examiner states that "[i]t is noted that entitlement to a filing date does not extend to subject matter which is not disclosed, but would be obvious over what is expressly disclosed. *Lockwood v. American Airlines Inc.*, 41 USPQ2d 1961 (Fed. Cir. 1977)." (Office Action at page 2). In *Lockwood*, the court stated that the question was not whether a claimed invention is an "obvious variant" of that which is disclosed in the specification but, rather, whether the specification necessarily discloses the particular invention. *See id.* at 1966. The written description requirement can be satisfied by "such descriptive means as words, structures, figures, diagrams, formulas, etc., that fully set forth the claimed invention." *Id.* "Although the exact terms need not be used *in haec verba*...." *Id.*

As discussed above, the instant claims are entitled to claim the benefit of priority application USSN 07/670,827 (filed March 18, 1991), because it provides sufficient written description and enablement for treating psoriasis, a TNFα-mediated human disease. Thus, the Examiners' statements are misplaced because treating TNFα-mediated disease, including

psoriasis, is disclosed in the priority application.

Enablement of Claims 1, 3-5 and 11-13 Under 35 U.S.C. § 112, first paragraph

The rejection of Claims 1, 3-5 and 11-13 under 35 U.S.C. § 112, first paragraph is maintained for reasons of record. The Examiner maintains that, in order to satisfy the enablement requirement under 35 U.S.C. § 112, first paragraph, with respect to the cA2 antibody, Applicants must either deposit the appropriate cell line that produces the cA2 antibody or provide the sequence of the entire immunoglobulin.

First, Applicants make clear that they have not deposited the cA2 antibody. The Examiner states that "[t]his appears to be inconsistent with the patented claims set forth in U.S. Patent No. 5,698,195 (Le et al.), wherein it is believed that the requirements for the deposit of the biological materials cA2 antibodies under 35 USC § 112, first paragraph, enablement, had been satisfied." (Office Action at page 2). A close and careful study of the prosecution history of Applicants' priority patent, U.S. Patent No. 5,698,195, reveals that on page 16 of the Amendment filed on March 14, 1997, Applicants replied to the 35 U.S.C. § 112, first paragraph enablement rejection, stating that:

> Since the Specification provides significant description of the properties (e.g., glycosylation, epitopic specificity and affinity) of the chimeric anti-TNF antibodies, the screening of antibodies which have the same or similar properties does not require undue experimentation. As such, no deposit is required. Please note that, to the best of knowledge of the undersigned, neither the c134A nor the c168A cell line has been deposited in the ATCC collection.

It is evident that this argument regarding enablement was found persuasive because a Notice of Allowance was issued on May 28, 1997 and the patent issued on September 16, 1997. Thus, Applicants have clearly and unambiguously stated in the prosecution history of the present application and the priority patent (U.S. Patent No. 5,698,195) that the cA2 antibody was not deposited.

Furthermore, the claims encompassing the cA2 antibody issued in related priority patents, such as U.S. Patent No. 5,919,452 and U.S. Patent No. 6,790,444. As is clear from the prosecution history of these patents, no deposit was necessary to satisfy the enablement requirement.

Second, in order to expedite prosecution, Applicants have canceled Claims 1, 5 and 11-13

and amended Claims 3 and 4. In regard to Claims 3 and 4, according to the Examiner, the cA2 antibodies "must be known and readily available to the public or obtainable by a repeatable method set forth in the specification." For the reasons of record, Applicants maintain that these claims are enabled because the cA2 antibodies can be obtained from publicly available material with only routine experimentation.

Applicants' written specification fully enables the practice of the claimed invention because the claimed cA2 antibodies can be made from readily available starting materials using methods that are well known in the art and taught in detail in the specification. As discussed above, and as detailed in the specification, the cA2 is derived from the A2 antibody. The A2 antibody was publicly available at least as of March 18, 1991. (See Vilcek Declaration" at ¶ 5)

Further, Applicants direct the Examiner's attention to the fact that the specification sets forth a great deal of information regarding the making of the cA2 antibody from the A2 antibody "by a repeatable method." For example, the sequences of the variable regions of the antibodies are disclosed in Figures 16A-16B. In addition, the specification teaches methods of producing the claimed cA2 antibodies according to the present invention (See instant Detailed Description at page 32, lines 7 through 24; page 34, line 10 through page 35, line 4; Examples I-IX teach the production, characterization and expression of the cA2 antibody). Examples X-XII teach assays for screening the cA2 antibody.

Further, as stated in the record, in considering the factors enumerated in *In re Wands*, which was submitted as Exhibit B with the Amendment filed February 25, 2004, Applicants' disclosure provides considerable direction and guidance on how to practice their invention, and presents numerous working examples. Thus, a person of skill in the art would not be subject to undue experimentation without a reasonable expectation of success in order to make and screen cA2 antibodies which would have these claimed elements. In addition, there was a high level of skill in the art at the time when the application was filed, and all of the methods needed to practice the invention were well known.

Thus, a deposit is not required and the entire immunoglobulin sequence is not required because the disclosure is sufficient to enable production of the claimed antibodies. No more is required. The Examiner has failed to present any evidence which suggests that anti-TNF antibodies with the claimed specificity are unusually difficult to isolate.

As discussed above and as maintained for the reasons of record, the instant Specification and figures, together with what was known and available in the art, provide ample teachings such

that one of skill in the art would not be subject to undue experimentation in order to make or use the claimed antibodies. Thus, the skilled artisan is enabled to make and use the claimed invention commensurate in scope with the claims.

Lastly, the Examiner has not rebutted Applicants' arguments submitted in the Amendment filed on February 25, 2004. According to the MPEP § 2164.05:

> Once the examiner has weighed all the evidence and established a reasonable basis to question the enablement provided for the claimed invention, the burden falls on applicant to present persuasive arguments, supported by suitable proofs where necessary, that one skilled in the art would be able to make and use the claimed invention using the application as a guide. *In re Brandstadter*, 484 F.2d 1395, 1406-07, 179 USPQ 286, 294 (CCPA 1973). The evidence provided by applicant need not be conclusive but merely convincing to one skilled in the art. (Emphasis found in original)
>
> ....
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> Applicant should be encouraged to provide any evidence to demonstrate that the disclosure enables the claimed invention.
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> ....
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> Once that evidence is submitted, it must be weighed with all other evidence according to the standards set forth above so as to reach a determination as to whether the disclosure enables the claimed invention.

In the present application Applicants have submitted arguments and evidence, including the Declaration by Dr. Vilcek, establishing that the disclosure is sufficient to enable production of the claimed antibodies. Further, priority patents, such as U.S. Patent No. 5,919,452 and U.S. Patent No. 6,790,444, have issued with claims encompassing the cA2 antibody because no deposit was necessary as the arguments regarding enablement were found persuasive. Thus, Applicants respectfully request that the Examiner weigh the evidence in accordance with the standard set forth in the MPEP.

Reconsideration and withdrawal of the rejection are respectfully requested.

Definiteness of Claims 1, 3-5, and 11-13 Under 35 U.S.C. § 112, second paragraph

The rejection of Claims 1, 3-5, and 11-13 as indefinite in the use of "cA2" as the sole means of identifying the claimed antibody is maintained for reasons of record. The Examiner maintains that "the use of 'cA2' antibody as the sole means of identifying the claimed antibody renders the claims indefinite because this designation is merely a laboratory designation which does not clearly define the claimed product, since different laboratories may use the same laboratory designation to define completely distinct cell lines."

In order to expedite prosecution, Claims 1, 5 and 11-13 have been canceled and Claims 3 and 4 have been amended. In regard to Claims 3 and 4, Applicants respectfully traverse this rejection. cA2 is not used as the sole means of identifying the antibody. The claims and specification provide a great deal of description regarding cA2's structure and properties. As amended, the claims explicitly state that cA2 is a "chimeric anti-TNFα monoclonal antibody." Further, the specification clearly discloses that the antibody is a chimeric anti-TNFα monoclonal antibody, and provides a detailed disclosure of the production, structure and function of cA2. (Specification at page 17, lines 2-8; page 19, lines 7-16; page 26, lines 21-28 and page 34, line 12 to page 35, line 4) For instance, Examples I-IX teach the production, characterization and expression of the cA2 antibody and Examples X-XII teach assays for screening the cA2 antibody.

The Examiner states that "[g]iven the ambiguity indicated above concerning satisfying the deposit of the cA2 antibody in U.S. Patents addressed above, this rejection is maintained." (Office Action at page 4). Applicants have clearly and unambiguosly stated that the cA2 antibody was not deposited. As discussed above, a deposit is not required because the disclosure is sufficient to enable production of the claimed antibodies. No more is required.

Further, a number of claims have issued which refer to the instant chimeric anti-TNFα monoclonal antibody as cA2. For example, the claims of related U.S. Patent No. 6,284,471, which has the same priority date and has a substantially identical specification as the instant application, recite cA2. (A copy of the claim set of U.S. Patent No. 6,284,471 was attached as "Exhibit F" in the Amendment filed on February 25, 2004).

For the reasons of record, Applicants maintain that "cA2" is recognized by those skilled in the art as a unique identifier of Applicants' chimeric anti-TNFα monoclonal antibody. A number of scientific articles and press releases refer to Applicants' claimed chimeric anti-TNFα monoclonal antibody as "cA2". (See Exhibits C and D, which were submitted with the Amendment filed on February 25, 2004). These references are representative of the general knowledge of one skilled in the art and demonstrate that the identifier "cA2" clearly defined the claimed product. Thus, the cA2 antibody is well known in the art.

The Examiner states that "applicant's reliance on published articles [Exhibits C and D] does not satisfy the requirement that cA2 particularly point out and distinctly claims the particular anti-TNF cA2 antibody asserted by applicant." (Office Action at page 4).

Applicants respectfully disagree and direct the Examiner's attention to MPEP §2173.02, which states that "definiteness of claim language must be analyzed, *not in a vacuum*, but in light

of: (A) the content of the particular application disclosure; (B) the teachings of the prior art; and (C) the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made (emphasis added)." Thus, in accordance with the MPEP, Exhibits C and D, which were submitted by Applicants with the Amendment filed February 25, 2005, are evidence that the term "cA2" is recognized by those skilled in the art as a unique identifier of Applicants' chimeric anti-TNFα monoclonal antibody.

In sum, cA2 does clearly define the claimed product. Applicants' disclosure provides a great deal of description regarding cA2's structure and properties. Further, the term "cA2" is recognized by those skilled in the art as a unique identifier of Applicants' chimeric anti-TNFα monoclonal antibody. Therefore, claims reciting the cA2 antibody, particularly as amended, are definite.

Reconsideration and withdrawal of the rejection are respectfully requested.

Novelty of Claims 1-2, 5 and 11-12 Under 35 U.S.C. § 102(e)

The rejection of Claims 1-2, 5 and 11-12 under 35 U.S.C. § 102(e) as being anticipated by Adair *et al.* (U.S. Patent No.: 5,994,510) is maintained for reasons of record.

In order to expedite prosecution, Claims 1, 5 and 11-13 have been canceled. Claim 2 was canceled in the previous Amendment filed on February 25, 2004. Therefore, the rejection is moot.

Nonobviousness of Claims 1, 3-5 and 7-13 Under 35 U.S.C. § 103(a)

The rejection of Claims 1, 3-5, and 7-13 as being unpatentable over Adair *et al.* (U.S. Patent No.: 5,994,510) in view of Le *et al.* (WO 92/16553) is maintained for reasons of record.

In order to expedite prosecution, Claims 1, 5 and 11-13 have been canceled and Claims 3 and 4 have been amended. In regard to Claims 3-4 and 7-10, Applicants respectfully disagree with the Examiner's position.

1. Le *et al.* and Adair *et al.* are not prior art.

For the reasons of record and for the reasons described herein with regard to priority, Applicants maintain that Le *et al.* (WO 92/16553) and Adair *et al.* are not prior art because the priority date of the subject application (March 18, 1991) precedes the date that Le *et al.* and

Adair *et al.* would be effective as prior art.

2. Adair does not teach or suggest Applicants' chimeric antibodies and teaches away from therapeutic use of any chimeric antibodies.

In regard to Adair *et al.*, the Examiner has invited Applicants to "distinguish the prior art TNFα-specific antibodies and the presently claimed TNFα-specific antibodies in methods of treating psoriasis." (Office Action at page 5.) Applicants claims are directed to fully chimeric anti-TNFα monoclonal antibody cA2. Adair *et al.* teaches the manufacture and use of humanized TNFα-specific antibodies. Further, Adair *et al.* teaches chimeric recombinant antibody molecules having antigen binding sites derived from the murine CB0006, CB0010, hTNF3 or 101.4. These antibody molecules were used as controls in experiments designed to demonstrate that humanized antibodies retain TNF binding properties comparable to control chimeric antibodies. Adair *et al.* does not teach the chimeric anti-TNFα monoclonal antibody cA2 or antibodies which competitively inhibit binding of TNFα to cA2. Moreover, Adair *et al.* does not teach Applicants' claimed sequences. For example, Adair *et al.* does not teach Applicants' claimed nucleic acid sequence (SEQ ID NO:2) and corresponding amino acid sequence (SEQ ID NO:3) of the cloned cA2 light chain variable region. Further, Adair *et al.* does not teach Applicants' claimed nucleic acid sequence (SEQ ID NO:4) and corresponding amino acid sequence (SEQ ID NO:5) of the cloned cA2 heavy chain variable region. Thus, the sequences disclosed in Adair *et al.* (Col. 14, Col. 15 and FIGS. 1-4) are not the same as the sequences of the variable regions of Applicants' claimed cA2 antibody as claimed by Applicants.

When determining patentability under 35 U.S.C. § 103, the prior art must be considered as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). The Examiner states that "Adair et al. teach methods of inhibiting...with TNFα-specific antibodies, including recombinant chimeric antibodies...." (Office Action at page 5). The Examiner's statement is incorrect because there is no teaching or suggestion in Adair *et al.* that chimeric antibodies can be used therapeutically. In fact, Adair teaches away from the

therapeutic use of any chimeric antibodies as evidenced by the following discussion in Adair *et al.*, Col. 2, lines 31-57:

> Early methods for humanizing Mabs involved production of chimeric antibodies in which an antigen binding site comprising the complete variable domains of one antibody is linked to constant domains derived from another antibody.
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> ....
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> Such humanized chimeric antibodies, however, still contain a significant proportion of non-human amino acid sequence, i.e., the complete non-human variable domains, and this may still elicit some HAMA response, particularly if administered over a prolonged period (citation omitted). In an alternative approach ...the complementarity determining regions (CDRs) of a mouse MAb have been grafted onto the framework regions of the variable domains of human immunoglobulin.... Such CDR-grafted humanized antibodies are much less likely to give rise to a HAMA response than humanized chimeric antibodies in view of much lower proportion of non-human amino acid sequence which they contain.

Adair *et al.* teaches away from producing chimeric antibodies for a therapeutic use because such antibodies may elicit a HAMA response and, thus, are not preferred. Rather, Adair *et al.* teaches the production of CDR-grafted humanized antibodies as preferred therapeutic antibodies. Thus Adair *et al.*, teaches away from producing the claimed chimeric monoclonal antibodies.

Further, the Examiner states that "[g]iven the inhibitory properties of the cA2 TNFα-specific antibodies taught by Le et al., one of ordinary skill in the art at the time the invention was made would have been motivated to substitute the cA2 anti-TNFα antibody specificity ... with TNFα-specific antibodies taught by Adair et al." (Office Action at page 6). Clearly the Examiner is mistaken because, as discussed above, Adair *et al.* does not teach or suggest that chimeric antibodies can be used therapeutically, and, in fact, teaches away from using such antibodies therapeutically. Thus, the Examiner's statement is incorrect.

3. Prior to the data presented in Applicants' application, there was no reason to believe that a substantial clinical benefit was possible with a chimeric anti-TNF antibody.

For the reasons of record, Applicants maintain that at the time of filing of the patent application, which claims the benefit of priority to U.S. Application Serial No. 07/670,827 (filed March 18, 1991), it was not known that such chimerization of murine antibodies could be done

successfully, or that chimeric antibodies provided superior results to murine antibodies for *in vivo* therapy. Further, the use of chimeric antibodies does not eliminate the immunogenic reaction. The presence of non-human sequences in humanized and chimeric antibodies indicates that immunogenicity would still be a concern in therapies involving such antibodies. In fact, most (if not all) chimeric antibodies, similar to murine antibodies, generate an immune response in the administered animal. Thus, it was unclear, prior to the data presented in this application, that substantial clinical benefit was possible with a chimeric anti-TNF antibody. In fact, the art at the time of the claimed invention taught away from the concept that chimerization prevents an immunologic response against administered antibodies. (See Exhibit I, which was submitted with the Amendment filed on February 25, 2004; See also Adair *et al.*, Col. 2, lines 43-48 and references cited therein).

4. There is objective evidence of non-obviousness.

For the reasons of record, Applicants maintain that, even assuming, *arguendo*, that a *prima facie* case of obviousness exists, which it does not, it would be overcome by the objective evidence of nonobviousness. The claimed invention has led to unexpected results in relation to the prior art, and has satisfied a long-felt need in the relevant field. The fact that others in the field had tried for years to achieve a result, yet had failed, is evidence that the invention would not have been obvious to those skilled in the art when it was invented.

The claimed compounds have been shown to have unexpected results in terms of the degree of success in clinical studies, particularly in studies involving patients with long-term refractory TNFα-mediated disease. The magnitude of these results in the treatment of a TNFα-mediated disease could not have been reasonably predicted from the prior art. (See Exhbit C and J, which were submitted with the Amendment filed February 25, 2004) This initial skepticism as to the merits of the invention by experts in the field further establishes the nonobviousness of this invention.

In sum, neither Le *et al.* nor Adair *et al.* are prior art. Even if Adair *et al.* were prior art, Adair *et al.* does not describe or suggest Applicants' chimeric anti-TNFα monoclonal antibodies, does not provide a reasonable expectation of achieving such antibodies having reduced

immunogenicity and a therapeutic benefit, and does not reasonably suggest that the unexpected and superior results achieved and described herein were possible. In fact, Adair *et al.* teaches away from therapeutic use of such antibodies, emphasizing their potential for eliciting a detrimental HAMA response. Therefore, the combination of Adair *et al.* and Le *et al.* does not render the claimed invention obvious. Moreover, the claimed invention has led to unexpected results and clearly satisfies a long felt but unsatisfied need. The claims are not obvious, and thus, reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Deirdre E. Sanders

Deirdre E. Sanders
Registration No. 42,122
Telephone: (978) 341-0036
Facsimile: (978) 341-0136

Concord, MA 01742-9133

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